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EXAMINER	
TON, THAIAN N	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/625,100	MUNNE, SANTIAGO	
	Examiner	Art Unit	
	THAIAN N. TON	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Amendment to the claims, filed 12/7/07, is found to be compliant and has been entered. Claims 5-8 are amended, pending and under current examination.

Applicants did not file any substantive remarks with the amendment, filed 12/7/07, therefore, the Examiner responds to the remarks filed 9/20/07.

The Sadowy Affidavit, filed 9/20/07, has been considered, but not found to be persuasive.

Claim Objections

The objection to claim 6 is withdrawn because Applicants' have amended the claim to recite "a stem cell".

The objection to claim 7 is withdrawn because "mitomycin" has been corrected.

The objection to claim 8 is withdrawn in view of Applicants' amendment which refers to "The method of claim 7".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7-8 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make

and/or use the invention. This rejection is maintained for reasons set forth in the prior Office action, mailed 3/23/07.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Applicants' Arguments. Applicants argue that Thomson does not teach the claimed invention, and that Applicants have marked a clear trail to making stem cells from trisomically derived disomic embryonic cell lines. See p. 6, 1st ¶. Applicants argue that using an antibody for embryonic stem cell markers does not require undue experimentation (p. 6, 2nd ¶). Applicants argue that because these antibodies are commercially available, testing the disomic cell lines does not require undue experimentation, and that all Wands factors are satisfied by simply identifying even one stem cell epitope on one cell population of a trisomically derived disomic cell line, such as testing to see if Tra-1-60 is expressed in any of the cells in the disomic cell lines. Applicants argue that this did not require any undue experimentation because the methods to test if this epitope was expressed are known in the art and provide the Sadowy affidavit to support these methods. See p. 7.

Response to Arguments. These arguments have been fully considered, but are not persuasive. The Examiner reiterates that pluripotent stem cells, such as embryonic stem cells, have specific, art-recognized properties. The Examiner's arguments are not solely directed to undue experimentation of testing whether Applicants' cells express specific markers (as suggested by Applicants). The prior rejection is directed to the fact that pluripotent stem cells have particular, art-recognized properties. Not only do these cells require expression of particular

markers, but that they have specific phenotypes, and characteristics, such as specific differentiation ability. The specification only discusses karyotypic analysis of the resultant disomic cell lines. Although Applicants' have tested Tra-1-60 as a potential marker in their cells, the Examiner responds that Tra-1-60 is not a marker that can be solely used to characterize a pluripotent cell. For example, Lajer *et al.* (**Int. J. Cancer**, 100: 244-246, 2002) teach that Tra-1-60 is additionally expressed in germ cell cancers. Thus, using a sole marker and karyotypic analysis would fail to identify a specific cell type. Applicants have not provided sufficient guidance or teachings with regard to the resultant cells that are produced by their method, such that one of skill in the art would recognize that they had the art-accepted characteristics of embryonic stem cells. For example, Applicants have not shown that the cells are capable of differentiation into cells of the three germ layers, which indicates the differentiation potential of the cells.

Applicants' Arguments. Applicants argue that they, "[C]an testify that I have assigned colleagues who are skilled in the art in making stem cells from these cell lines with only the specification and references detailed in this patent application and they have successfully isolated stem cells (RG44, RG56, RG92, RG93, RG94, RGK230) that have the characteristic epitopes of stem cells (SSEA-1, SSEA-3, SSEA-4, TRA 1-60, TRA 1-81, OCT 4, alkaline phosphatase)." See page 4, 2nd ¶ of the Response.

Response to Arguments. These arguments are not persuasive. This does not represent an appropriate affidavit to provide evidence of record. Applicants have not provided the appropriately signed affidavit with regard to this aspect of the rejection. Additionally, there is no specific guidance to show that any of the cell lines (RG44, RG56, RG92, RG93, RG94, RGK230) are cell lines that are produced by the same methods as those disclosed in the as-filed specification, or that any of these cell lines are the ones that are disclosed in the as-filed specification. Applicants provide a micrograph that they feel shows the nexus between disomic

cells characterized by karyotyping and FISH analysis, and the derived stem cell population characterized by Tra-1-60 epitope using a rhodamine labeled ligand (p. 8 of the Response). Applicants argue that the specification does provide sufficient guidance to enable the claimed invention. The Examiner responds that Applicants have not provided specific guidance between the cell lines that they discuss, the methods that are used to produce these cell lines, and the specific characteristics of these cell lines such that one could reasonable conclude that the stem cell lines that Applicants recite, and the characteristics of the cell line(s) that are disclosed in the working example are one in the same. The Sadowy declaration discusses analysis of trisomic embryos, the plating of blastocysts on human fibroblast feeder cells, and the passage of the resultant colonies and analysis of the resultant cells which showed that the specific cell line, after 1 month of culture continued to have 3/22 cells had trisomy 18, 0/22, trisomy 16 and 14/22 were disomic for all chromosomes tested. The Declaration further teaches Tra-1-60 binding to cells. These arguments are not persuasive. The Declaration does not show that the cells that bind Tra-1-60 are disomic, there is no karyotypic analysis of the cells. Furthermore, the Declaration does not show any other characterization of the cells other than the potential expression of this particular marker, which the Examiner has shown can be expressed in other cell types. There is no indication that the cells are undifferentiated; merely that they express Tra-1-60. The Declaration is not persuasive.

Applicants state that they are currently working on further identification of the cells by injecting them into mice to test their differentiation capacity (p. 9, Response). These arguments are not persuasive because Applicants have provided no evidence with regard to the differentiation capacity of their cells.

Applicants provide no substantive remarks with regard to the remainder of the rejection from the prior Office action, mailed 3/23/07. Therefore, this rejection is maintained. Particularly:

1. The working examples do not provide sufficient guidance or teachings with regard to the characterization of the embryonic cells that are produced by the claimed method. In particular, the specification provides no guidance, other than the karyotypic analysis of the resultant disomic cells. There is no guidance with regard to if the cells are pluripotent, express appropriate markers, or have any of the art-recognized characteristics of embryonic stem cells. As stated in the prior Office action,

2. The specification only provides a contemplated use with regard to embryonic **stem** cells. See, for example, page 3, paragraph 8 of the specification, which discusses the isolation of stem cells from the resultant diploid cells. There are no teachings or guidance provided by the specification with regard to the isolation of non-embryonic stem cells (i.*e.*, "embryonic cells", see claim 7, step (f)) from the diploid cell lines produced, or what these embryonic cells (which are not stem cells) would be used for.

The standard, under 112, 1st ¶, for enablement is that the specification must provide guidance on how to make and use the claimed invention. One of skill would not be able to make embryonic *stem* cells from the teachings of the specification, because there is no guidance with regard to the disomic cell lines that are produced from the trisomic embryos, in particular, that they have any of the art-recognized characteristics of embryonic stem cells. One of skill would not know how to make and use embryonic cells that are not stem cells that are encompassed by the claims, because the specification provides no guidance with regard to the isolation or characterization of these cells which are not stem cells, or what the cells would be used for.

Accordingly, in view of the state of the art of embryonic stem cells, namely the specific, art-recognized characteristics of such cells, the lack of teaching, guidance or characterization of cells produced by the claimed method, other than karytotypic analysis of the cells, the unpredictable state of the art of producing

embryonic stem cells, and the lack of guidance or teaching provided by the specification to overcome these unpredictibilities, the lack of teaching or guidance with regard to how to make embryonic cells that are not stem cells, it would have required undue experimentation for one of skill in the art to make and use the claimed disomic cell lines.

Claim Rejections - 35 USC § 112

The prior rejection of claim 6 is withdrawn under 112, 2nd paragraph, in view of Applicants' amendment which now recites "said disomic cell line".

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7-8 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants have not amended the claims with respect to the prior rejections, therefore these rejections are maintained.

Claim 7 is indefinite for the following reasons:

1. Part (c) of the claim refers to "said medium". It is unclear which medium this refers to, because step (b) refers to using "DMEM without sodium pyruvate, glucose 4500 mgL-1 supplemented with 20% fetal bovine serum, 0.1 mM -mercaptoethanol, 1% non-essential amino acids, 1 mM L-glutamine, 50 units ml L-1 penicillin." Therefore the only "medium" in part (b) is the DMEM. If Applicants intend to include the other components recited in part (b), it is suggested that Applicants' amended the claim to recite, for example, "medium comprising…".

2. The claim recites the limitation "said embryonic cell lines" in part (e) of the claim. There is insufficient antecedent basis for this limitation in the claim. Claim 8 depends from claim 7.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Applicants provide the same remarks for both rejections of record; therefore, the Examiner addresses these arguments below:

Applicants' Arguments. Applicants argue that their stem cell lines are uniparental, whereas the stem cell lines taught by Thomson and Shamblott are not, because the stem cell lines that are taught by Thomson and Shamblott are derived from euploid embryos, and therefore have one chromosome set from each parent, and each allele must be expressed in competition with its corresponding partner. Applicants argue that their uniparental stem cell lines have two identical allelic copies for each gene for the chromosome affected, and that Applicants are currently running experiments to demonstrate the uniparental nature of the cell lines. Applicants argue that their cells differ genotypically in character from the cells taught in the art, because they are "completely homozygotic" for chromosomes affected, and therefore, may have stem cell epitopic markers in twice the number making them easier to identify, detect and isolate and that this depends if the uniparental chromosome has genes for stem cell epitopes for which antibodies or binding ligands exist. See pp. 10-11 of the Response.

Response to Arguments. Applicants are arguing limitations that are not found within the claims. There is no requirement with regard to the uniparental/biparental nature of the cells. There is no requirement that the cells have one chromosome set from one parent. Applicants have not provided guidance to show that their cells have this characteristic because they are still running

experiments to demonstrate this property. The as-filed disclosure discusses various ways in which a trisomic cell line can revert to disomic, such as anaphase lag, non-disjuntion and chromosome demolition. Anaphase lag results in a disomic cell and a trisomic daughter cell. Non-disjunction results in a viable disomic cell and one lethal quadrisomic cell. Chromosome demolition results in deliberate fragmentation of one of the three chromosomes during metphase or anaphase, resulting in two disomic daughters. See p. 5 of the Specification.

Applicants' trisomic embryos have two copies of chromosomes from one parent, and one copy from another parent because these embryos are produced by fertilization. Therefore, the destruction of one of three copies of chromosomes could be from the parent contributing two copies (thus, providing an embryo with one copy from each parent, therefore, a biparental cell line), or the loss of one copy from the parent contributing one copy (thus, providing an embryo with two copies of a chromosome from one parent, *i.e.,* uniparental). However, there is no guidance in the specification as to which scenario occurs, or if one scenario occurs in a predictable fashion with regard to the resultant cell lines, or how the resultant, disomic cell line differs from any other disomic cell line. A disomic cell line would be karyotypically normal, and have the same genome as any other normal cell. Applicants have provided no guidance to show their cells are wholly homozygotic. They provide no guidance to show that their cells have stem cell epitopic markers in twice the numbers. These recitations are not found within the claims. The claims do not distinguish Applicants' cells from those of the art.

The Examiner maintains that the claims are product-by-process claims, wherein the specification provides no guidance to show differences between Applicant's cell lines and disomic cell lines taught by either Thomson or Shamblott. The requirement for the claims is that the cell lines are disomic, and this is fulfilled by the cited references.

Applicants' arguments with regard to Shamblott's normal disomic cell lines requiring de-differentiation to become totipotent is not persuasive (p. 10, 2nd ¶ of the Response). The claims do not require the cells to be totipotent, merely that the cell line is disomic. Additionally, Applicants have not shown their cells to be totipotent, therefore this characteristic is neither recited nor required. Applicants' arguments that Shamblott's cells are heterozygotic containing both alleles from both parents are not persuasive for reasons set forth above.

Claims 5 and 6 stand rejected, as applied to now cancelled claims 1-2, under 35 U.S.C. 102 (b) as being anticipated by Thomson [WO 96/22362, published 25 July 1996]. This rejection is maintained for reasons of record, advanced in the prior Office action, mailed 11/23/05 and 3/23/07.

Thomson teach the isolation and purification of primate embryonic stem cells that are capable of indefinite proliferation *in vitro* in an undifferentiated state, are capable of differentiation to derivatives of all three embryonic germ layers, and maintain a normal karyotype throughout prolonged culture. The pluripotent cells are negative for SSEA-1, positive for the SSEA-3 marker, positive for the SSEA-4 marker, TRA-1-60, TRA-1-81 and alkaline phosphatase. Thomson teach that the primate cells can continue to proliferate in an undifferentiated state for at least one year. See p. 7, lines 9-32. Thomson teach that tumors formed after injection of rhesus ES cells into the hindleg muscles of SCID mice [see Figure 5].

Accordingly, Thomson *et al.* anticipate the claimed invention because they teach a disomic cell line, and particularly, a disomic, embryonic stem cell line.

Claims 5 and 6 stand rejected, as applied to now cancelled claims 1-2, as being anticipated by Shamblott *et al.* [**PNAS**, 95:13726-13731 (1998)].

Shamblott teach that human pluripotent stem cells were isolated from gonadal ridges and mesenteries of 5- to 9-week postfertilization human embryos. Cells were cultured and subsequently passaged onto a mouse STO fibroblast feeder

layer. Shamblott teach that embryoid bodies were collected from cultures and immediately embedded or replated into single wells [under conditions using mouse embryo fibroblasts, human fetal fibroblasts, or gelatin-coated tissue culture, see p. 13729, 1st column, 1st full ¶] and cultured for 14 days in the absence of hrLIF, hrbFGF and forskolin. See pp. 13726-13727, *Materials and Methods*. They teach that immunohistochemical analysis of embryoid bodies demonstrated that the cells could differentiate into a variety of cell types, including derivatives of the three embryonic germ layers. See p. 13729, 2nd column, 1st full ¶. They teach that these cellsl are karyotypically normal (see Abstract, and Material and Methods).

As Shamblott *et al.* teach a disomic cell line, and in particular, an disomic, embryonic stem cell line, they anticipate the claimed invention.

Claims 5 and 6 stand rejected, as applied to now cancelled claims 1-2, as being anticipated by Thomson *et al.* (**PNAS**, 92:7844-7848 (August 1995)).

Thomson *et al.* teach pluripotent primate embryonic stem cells, isolated from a rhesus monkey blastocyst. They teach that these cells remain undifferentiated in culture in continuous passage, maintain a normal karyotype, express appropriate cell markers [alkaline phosphatase, SSEA-3, SSEA-4, TRA-160-, TRA-1-81] and, when injected into SCID mice, they consistently differentiate into derivatives of all three germ layers. See *Abstract* and p. 7845-7846.

Accordingly, as Thomson teach a disomic stem cell line, they anticipate the claimed invention.

Claims 5 and 6 stand rejected, as applied to now cancelled claims 1-2, as being anticipated by Thomson [**U.S. Pat. No.** 6,200,806 B1, March 13, 2001].

Thomson teach the preparation of a primate embryonic stem cell line that has expresses the cell surface markers characteristic of embryonic stem cells, have normal karyotypes, are able to proliferate in an undifferentiated state in continuous

culture, and the ability to differentiate into all tissues derived from all three embryonic germ layers (see Abstract and claims).

Thus, because Thomson teach a karyotypically normal, disomic human embryonic stem cell line, they anticipate the claimed invention.

Conclusion

No claim is allowed.

This action is a **final rejection** and is intended to close the prosecution of this application. Applicant's reply under 37 CFR 1.113 to this action is limited either to an appeal to the Board of Patent Appeals and Interferences or to an amendment complying with the requirements set forth below.

If applicant should desire to appeal any rejection made by the examiner, a Notice of Appeal must be filed within the period for reply identifying the rejected claim or claims appealed. The Notice of Appeal must be accompanied by the required appeal fee of $255.

If applicant should desire to file an amendment, entry of a proposed amendment after final rejection cannot be made as a matter of right unless it merely cancels claims or complies with a formal requirement made earlier. Amendments touching the merits of the application which otherwise might not be proper may be admitted upon a showing a good and sufficient reasons why they are necessary and why they were not presented earlier.

A reply under 37 CFR 1.113 to a final rejection must include the appeal from, or cancellation of, each rejected claim. The filing of an amendment after final rejection, whether or not it is entered, does not stop the running of the statutory period for reply to the final rejection unless the examiner holds the claims to be in condition for allowance. Accordingly, if a Notice of Appeal has not been filed properly within the period for reply, or any extension of this period obtained under either 37 CFR 1.136(a) or (b), the application will become abandoned.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to THAIAN N. TON whose telephone number is (571)272-0736. The examiner can normally be reached on 9-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Thaian N. Ton/
Primary Examiner, Art Unit 1632